PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 January 2001 (08.01.01)	
International application No. PCT/EP00/02468	**Applicant's or agent's file reference** ML/B45175
International filing date (day/month/year) 17 March 2000 (17.03.00)	**Priority date** (day/month/year) 19 March 1999 (19.03.99)
Applicant CAPIAU, Carine et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 September 2000 (21.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Jean-Marc Vivet
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

EP0002468

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 39/385, 39/39, 39/02, 39/005, 39/116, A61P 31/04

A2

(11) International Publication Number: **WO 00/56360**

(43) International Publication Date: 28 September 2000 (28.09.00)

(21) International Application Number: PCT/EP00/02468

(22) International Filing Date: 17 March 2000 (17.03.00)

(30) Priority Data:

9906437.0	19 March 1999 (19.03.99)	GB
9909077.1	20 April 1999 (20.04.99)	GB
9909466.6	23 April 1999 (23.04.99)	GB
9916677.9	15 July 1999 (15.07.99)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM BIOLOGICALS S.A. [BE/BE]; Rue de l'Institut 89, B–1330 Rixensart (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CAPIAU, Carine [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE). DESCHAMPS, Marguerite [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE). DESMONS, Pierre, Michel [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE). LAFERRIERE, Craig, Antony, Joseph [CA/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE). POOLMAN, Jan [NL/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE). PRIEELS, Jean–Paul [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE).

(74) Agent: GIDDINGS, Peter, John; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: VACCINE

(57) Abstract

The present invention relates to the field of bacterial polysaccharide antigen vaccines. In particular, the present invention relates to bacterial polysaccharides conjugated to protein D from *H. influenzae*.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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ZW	Zimbabwe

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(19) World Intellectual Property Organization
International Bureau

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(10) International Publication Number
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(30) Priority Data:

9906437.0	19 March 1999 (19.03.1999)	GB
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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM BIOLOGICALS S.A.** [BE/BE]; Rue de l'Institut 89, B-1330 Rixensart (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CAPIAU, Carine** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **DESCHAMPS, Marguerite** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **DESMONS, Pierre, Michel** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **LAFERRIERE, Craig, Antony, Joseph** [CA/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **POOLMAN, Jan** [NL/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **PRIEELS, Jean-Paul** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE).

(74) Agent: **GIDDINGS, Peter, John**; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
25 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/56360 A3

(54) Title: VACCINE AGAINST ANTIGENS FROM BACTERIAE

(57) Abstract: The present invention relates to the field of bacterial polysaccharide antigen vaccines. In particular, the present invention relates to bacterial polysaccharides conjugated to protein D from *H. influenzae*.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/02468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/385 A61K39/39 A61K39/02 A61K39/005 A61K39/116
A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 32963 A (HENRY M JACKSON FOUNDATION FOR ;SMITHKLINE BEECHAM BIOLOG (BE)) 24 October 1996 (1996-10-24)	1,2,11, 20-23
Y	the whole document especially page 8 lines 22-27, example 9-12	3-8, 12-19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	30/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Stein, A

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/02468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	AKKOYUNLU MUSTAFA ET AL: "The acylated form of protein D of Haemophilus influenzae is more immunogenic than the nonacylated form and elicits an adjuvant effect when it is used as a carrier conjugated to polyribosyl ribitol phosphate." INFECTION AND IMMUNITY, vol. 65, no. 12, December 1997 (1997-12), pages 5010-5016, XP002149964 ISSN: 0019-9567 the whole document	1,2,11
Y	LEE C J ET AL: "Immunologic epitope, gene, and immunity involved in pneumococcal glycoconjugate." CRITICAL REVIEWS IN MICROBIOLOGY, vol. 23, no. 2, 1997, pages 121-142, XP000946772 the whole document, especially page 132 column 2 line 27 - page 135 column 2 line 18	4-8
Y	ESKOLA J ET AL: "Reactogenicity and immunogenicity of combined vaccines for bacteraemic diseases caused by Haemophilus influenzae type b, meningococci and pneumococci in 24-month-old children." VACCINE, vol. 8, no. 2, April 1990 (1990-04), page 107-10 XP002149965 the whole document	3,12-15
Y	WO 96 33739 A (SMITHKLINE BEECHAM BIOLOG ;GARCON NATHALIE MARIE JOSEPHE (BE); FRI) 31 October 1996 (1996-10-31) cited in the application page 1, line 1 -page 3, line 21 claims 1,5,8-10,12	16-19
Y	DE VELASCO E ALONSO ET AL: "Synthetic peptides representing T-cell epitopes act as carriers in pneumococcal polysaccharide conjugate vaccines." INFECTION AND IMMUNITY, vol. 63, no. 3, 1995, pages 961-968, XP002149966 ISSN: 0019-9567 the whole document	18,19

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/02468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ALEXANDER JANET E ET AL: "Immunization of Mice with Pneumolysin Toxoid Confers a Significant Degree of Protection against At Least Nine Serotypes of Streptococcus pneumoniae." INFECTION AND IMMUNITY, vol. 62, no. 12, 1994, pages 5683-5688, XP002149967 ISSN: 0019-9567 page 5683, column 1, line 26 -column 2, line 8 page 5687, column 1, line 51 - line 58 ---	5-8
A	VERHEUL A F M (REPRINT) ET AL: "MENINGOCOCCAL LIPOPOLYSACCHARIDES - VIRULENCE FACTOR AND POTENTIAL VACCINE COMPONENT" MICROBIOLOGICAL REVIEWS, vol. 57, no. 1, 1993, pages 34-49, XP000946786 page 39, column 2, line 4 - line 49 ---	9,10
P,X	WO 99 33488 A (DALEMANS WILFRIED L J ;PRIEELS JEAN PAUL (BE); SMITHKLINE BEECHAM) 8 July 1999 (1999-07-08) the whole document -----	1-4, 16-23

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 00/02468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632963 A	24-10-1996	AU 716806 B	09-03-2000
		AU 5485696 A	07-11-1996
		CA 2218385 A	24-10-1996
		EP 0824360 A	25-02-1998
		JP 11508225 T	21-07-1999
WO 9633739 A	31-10-1996	AP 771 A	07-10-1999
		AT 186842 T	15-12-1999
		AU 693022 B	18-06-1998
		AU 5334596 A	18-11-1996
		AU 699213 B	26-11-1998
		AU 6987398 A	23-07-1998
		BG 101995 A	30-11-1998
		BR 9608199 A	18-05-1999
		CA 2217178 A	31-10-1996
		CN 1182370 A	20-05-1998
		CZ 9703379 A	18-03-1998
		DE 69605296 D	30-12-1999
		DE 69605296 T	18-05-2000
		EP 0822831 A	11-02-1998
		EP 0884056 A	16-12-1998
		EP 0955059 A	10-11-1999
		ES 2140076 T	16-02-2000
		GR 3031912 T	29-02-2000
		HU 9801560 A	28-10-1998
		JP 11504020 T	06-04-1999
		NO 974859 A	21-10-1997
		NZ 305365 A	28-05-1999
		PL 322968 A	02-03-1998
		SI 822831 T	29-02-2000
		SK 144297 A	06-05-1998
		ZA 9602612 A	29-08-1996
WO 9933488 A	08-07-1999	AU 2419099 A	19-07-1999
		AU 2419199 A	19-07-1999
		WO 9933868 A	08-07-1999
		EP 1039930 A	04-10-2000
		EP 1040123 A	04-10-2000
		NO 20003302 A	18-08-2000
		NO 20003303 A	04-08-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DM/MJWD/B45175		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/02468	17/03/2000	19/03/1999
International Patent Classification (IPC) or national classification and IPC A61K39/385		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/09/2000	08.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrero, M Telephone No. +49 89 2399 8542

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02468

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-72	as originally filed				

Claims, No.:

1-18	as received on	24/04/2001	with letter of	23/04/2001	

Drawings, sheets:

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☒ the claims, Nos.: 9 and 15

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 18 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-18

	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION III

Claim 18 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 In view of the priority documents pertaining to the present application, the international patent application WO 99/33488 (publication date 08.07.99), cited in the International Search Report under the "P" category, is not to be regarded as state of the art according to Rule 64 (1) PCT as the claimed date of priority of 19.03.99 can be allowed for the relevant parts of the application.

Nevertheless, the aforementioned WO 99/33488 (filed on 18.12.98) appears to disclose immunogenic compositions and methods for their production, vaccines and therapeutic uses falling under the scope of present Claims 1-3 and 11-18 (see Examples 2, 3 and 5 of WO 99/33488). This document is therefore brought to the Applicant's attention in view of the provisions of Article 54(3) and (4) EPC.

2.2 The following documents have been considered for the purposes of this report:

D1: WO 96/32963
D2: Akkoyunlu, M. et al (1997) Infection and Immunity **65**:5010-5016
D3: Lee, C.J. et al (1997) Critical Reviews in Microbiology **23**:121-142
D4: Eskola, J. et al (1990) Vaccine **8**:107-110
D5: WO 96/33739 (also cited in the application)

2.3 D1 relates to the use of bacterial lipoproteins in inducing humoral immunity in response to polysaccharide antigens. For this purpose D1 discloses preferred immunogenic conjugates consisting of *Haemophilus influenzae* lipoprotein D

(LPD) conjugated to polysaccharide antigen derived from *Streptococcus pneumonie* serotypes 6B or 14 or to capsular polysaccharide antigen from *Haemophilus influenzae b* (Hib). In one of the two described methods for preparing these conjugates, the LPD is directly covalently attached to the polysaccharide after CDAP activation of the polysaccharide. In a passive mouse protection experiment full protection was observed with anti-PS 6B-LPD conjugates (cf page 7, lines 17-26 and Example 12 on pages 20-24).

D2 discloses vaccines comprising polysaccharide conjugate antigens consisting of protein D of *Haemophilus influenzae* directly conjugated to capsular polysaccharide antigen (PRP) derived from *Haemophilus influenzae* type *b* (Hib) (cf **PRP vaccines** on the left column of page 5011). These vaccines were protective in an experimental rat model of Hib strain-Minn A-induced otitis media (cf last 22 lines of the discussion on the right column of page 5015).

However, neither the use of LPD nor protein D from *Haemophilus influenzae* as a carrier for multiple polysaccharide antigens in the same composition is either disclosed or suggested in any of the aforementioned D1 or D2.

D3 refers to polyvalent pneumococcal polysaccharide-protein conjugate vaccines (cf Table 3 on page 134), to protective antibody-eliciting *S. pneumonie* protein antigens (pneumolysin, PspA, PsaA) and to their use in a combined mixture or in the form of polysaccharide-protein conjugates (see on page 135, the second paragraph on the left column and the paragraph bridging the left and right columns).

D4 analyses the reactogenicity and immunogenicity of combined vaccines consisting of Hib conjugate vaccine (PRP-diphtheria toxoid), a pneumococcal (PNC) 23-valent vaccine and tetravalent (MenACYW) or divalent (MenAC) meningococcal vaccines and suggests a preferred vaccine combination containing all these components, in particular T-dependent conjugated forms of both meningococcal and pneumococcal vaccines that could be given in infancy together with a Hib conjugate (cf last paragraph in the left column of page 110).

D5 discloses the use of 3D-MPL and saponin as adjuvants in vaccines containing meningococcal or pneumococcal polysaccharide antigens (cf page 1, lines 8-16, page 2, lines 19-23 and page 3, first paragraph)

2.4 The undesirable carrier-induced epitope suppression effect associated with the use of T-cell highly immunogenic protein carriers as TT (tetanus toxoid) or DT (diphtheria toxoid) constitutes a drawback well known to the skilled person confronted with the formulation of vaccines based on polysaccharide antigens of pathogenic bacteria (see description page 6, line 21 to page 8, line 3) .

Contrary to the apparent results to be expected, the data provided in the application (see Examples) seemingly substantiate that protein D from *Haemophilus influenzae* is particularly suitable for minimising such epitopic suppression effects in combination vaccines where multiple polysaccharide antigens are conjugated onto protein D (cf application page 25, lines 5-16 and page 27, lines 4-8).

The advantageous property associated with the use of protein D from *Haemophilus influenzae* as a carrier for multiple polysaccharides in the same composition disclosed in the application seems to be non-obviously derivable from any of the prior art documents cited in the International Search Report, either if they are considered alone or in combination. Accordingly, present Claims 1-18 would in principle appear to relate to novel and inventive subject-matter which satisfies the criteria set forth in Art. 33(2) and (3) PCT.

2.5 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present Claims 15 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States.

The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

2. The terms "Sepharose" (page 32, lines 12 and 16), "Sephacryl" (page 33, line 8; page 63, line 25 and page 66, line 29), "Maxisorp Nunc" (page 47, line 8) and "Tween" (page 47, line 11) appear to be registered trade marks, but have not been acknowledged as such.

SECTION VIII

1. For the sake of clarity (Art. 6 PCT) the immunogenic composition according to Claim 1 should have been defined, for instance, as: "An immunogenic composition comprising a plurality of (different) polysaccharide conjugate antigens, each conjugate consisting of a polysaccharide antigen derived from a pathogenic bacterium ...".

2. The embodiments of the invention identified in the present application as aspects (A) and (B), which are described on page 1, lines 6-11; page 2, line 27-page 6, line 7; page 8, line 15-page 10, line 17; page 10, line 27-page 18, line 26 and page 18, line 27-page 22, line 15 do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

3. It would appear that on page 53, lines 1-2 were meant to read "... in some clinical trials, that is, anti-polysaccharide antibody is insufficient to protect...".

Claims

1. A polysaccharide conjugate antigen comprising a polysaccharide antigen derived from a pathogenic bacterium conjugated to protein D from *Haemophilus influenzae* or a protein D fragment thereof.

2. A polysaccharide conjugate as claimed in claim 1 wherein the polysaccharide antigen is selected from the group consisting of: Vi polysaccharides from *Salmonella typhi*, meningococcal polysaccharides, polysaccharides and modified polysaccharides of group B meningococcus, polysaccharides from *Staphylococcus aureus*, polysaccharides from *Streptococcus agalactiae*, polysaccharides from *Streptococcus pneumoniae*, polysaccharides from Mycobacteria, polysaccharide from *Cryptococcus neoformans*, lipopolysaccharides of non-typeable *Haemophilus influenzae*, capsular polysaccaharide from *Haemophilus influenzae b*, lipopolysaccharides of *Moraxella catharralis*, lipopolysaccharides of *Shigella sonnei*, and lipopeptidophosphoglycan (LPPG) of *Trypanosoma cruzi*.

3. An immunogenic composition comprising a plurality of polysaccharide conjugate antigens as claimed in claims 1 or 2.

4. An immunogenic composition as claimed in claim 3 comprising *Streptococcus pneumoniae* polysaccharide antigens from at least four *Streptococcus pneumoniae* serotypes.

5. An immunogenic composition as claimed in claims 3 or 4 additionally comprising at least one *Streptococcus pneumoniae* protein antigen.

6. The immunogenic composition of claim 5, wherein the protein antigen is an outer surface protein or a secreted protein of *Streptococcus pneumoniae* or immunologically functional equivalents thereof.

7. The immunogenic composition of claims 5 or 6, wherein the protein antigen is a toxin, adhesin or lipoprotein of *Streptococcus pneumoniae* or immunologically functional equivalents thereof.

8. The immunogenic composition of claims 5-7, wherein the protein antigen, or immunologically functional equivalent thereof, is selected from the group consisting of: pneumolysin, PspA or transmembrane deletion variants thereof, PspC or transmembrane deletion variants thereof, PsaA or transmembrane deletion variants thereof, glyceraldehyde-3-phosphate dehydrogenase, and CbpA or transmembrane deletion variants thereof.

9. An immunogenic composition comprising a *Neisseria meningitidis* - protein D polysaccharide conjugate antigen.

10. An immunogenic composition as claimed in claim 9 wherein the polysaccharide antigen is derived from *N. meningitidis* serotypes A, C or Y or a combination thereof.

11. An immunogenic composition comprising a *Haemophilius influenzae* b - protein D polysaccharide conjugate antigen.

12. An immunogenic composition comprising conjugated capsular polysaccharides of *Haemophilius influenzae* b, meningococcus C and meningococcus Y, wherein the carrier protein for at least one of the polysaccharides is protein D from *H. influenze*.

13. An immunogenic composition comprising conjugated capsular polysaccharides of *Streptococcus pneumoniae*, *Haemophilius influenzae* b, meningococcus C and meningococcus Y, wherein the carrier protein for at least one of the polysaccharides is protein D from *H. influenze*.

14. The immunogenic composition of claims 12 and 13, wherein all of the polysaccharide antigens are conjugated to protein D, with the proviso that the polysaccharide from *Haemophilius influenzae* b is conjugated to tetanus toxoid.

15. The immunogenic composition of claims 12 and 13, wherein all of the polysaccharide antigens are conjugated to protein D.

16. An immunogenic composition as claimed herein additionally comprising an adjuvant.

17. An immunogenic composition as claimed in claim 16 wherein the polysaccharide – protein D conjugate antigen is adsorbed onto aluminium phosphate.

18. An immunogenic composition as claimed in claim 16 wherein the adjuvant is a preferential inducer of a TH1 response.

19. An immunogenic composition as claimed in claim 18, wherein the adjuvant comprises at least one of the following: 3D-MPL, a saponin immunostimulant, or an immunostimulatory CpG oligonucleotide.

20. An immunogenic composition as claimed herein for use as a medicament.

21. A vaccine comprising the immunogenic composition of claims 3-19.

22. A method of producing an immunogenic composition to a pathogenic bacterium comprising the steps of:

isolation of a polysaccharide antigen from said pathogenic bacterium;
activation of the polysaccharide; and
conjugation of the polysaccharide to protein D.

23. A method of treating a patient suffering from, or susceptible to, infection from a pathogenic bacterium comprising administering an effective amount of an immunogenic composition as claimed herein.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
SMITHKLINE BEECHAM PLC
Corporate Intellectual Property
Attn. Giddings, Peter John
Two New Horizons Court
Brentford
Middlesex TW8 9EP
UNITED KINGDOM

Applicant's or agent's file reference ML/B45175	Date of mailing *(day/month/year)* 30/10/2000
International application No. PCT/EP 00/ 02468	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.	International filing date *(day/month/year)* 17/03/2000

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Catherine Humbert

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
ML/B45175		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 02468	17/03/2000	19/03/1999

Applicant

SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   VACCINE AGAINST ANTIGENS FROM BACTERIAE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.